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Disorders of the Thyroid in the Newborn and Infant

Introduction

During the past three decades, our understanding of thyroid system ontogenesis and thyroid function and dysfunction in the fetus and newborn has advanced dramatically. Screening of newborns for congenital hypothyroidism is routine throughout most of the industrialized world, and we have increasing access to and information regarding fetal and neonatal thyroid function for management of complicated pregnancies and for assessment and management of thyroid dysfunction in the premature and term infant. Molecular technology has provided new insights and diagnostic approaches to inborn defects in thyroid hormone metabolism. This chapter is a review of current understanding of thyroid system ontogenesis and the classification and management of the disorders of thyroid function in the fetus and newborn infant.

Thyroid System Embryogenesis

Anatomic development of the hypothalamic-pituitary-thyroid system occurs during the first trimester of gestation.[1,2] The human thyroid gland develops from a median anlage derived from the primitive pharyngeal floor and paired lateral anlagen from the fourth pharyngiobronchial pouch. These structures are visible by days 16 to 17 of gestation. By 50 days, the median and lateral anlagen have fused, the buccal stalk has ruptured, and the thyroid gland has migrated to its definitive location in the anterior neck. By 70 days of gestation, iodide concentration and thyroglobulin synthesis can be demonstrated within the thyroid gland.

The anterior pituitary gland is derivative of the primitive buccal cavity (Rathke's pouch), and its embryological development parallels that of the thyroid anlagen. By the fifth week, Rathke's pouch makes contact with a funnel-

shaped diverticulum of the third cerebral ventricle, the infundibular process, which has grown ventrally. By 12 weeks, the buccal connection is obliterated by the developing sphenoid bone, and the pituitary gland becomes partially encapsulated within a bony cavity, the sella turcica. Secretory granules can be identified within the differentiating pituitary cells at 10 to 12 weeks, and thyroid-stimulating hormone (TSH [thyrotropin]) is identifiable by bioassay and immunoassay. The hypothalamus can be discerned histologically by 35 to 40 days, and the hypothalamic nuclei become progressively delineated at 80 to 100 days. Thyrotropin-releasing hormone (TRH) and somatostatin are detectable in hypothalamic tissue by 70 to 80 days.

Placental Iodine and Thyroid Metabolism

Adequate quantities of iodide are essential for fetal thyroid hormone synthesis, and during pregnancy the fetal thyroid competes with the maternal gland for available iodine supply. In geographical areas of iodine deficiency, this competition is increased by the increased size and iodine-concentrating activity of the maternal thyroid gland. In lower species, the placenta compensates this maternal advantage to some degree by actively transporting iodide in the maternal-to-fetal direction. Studies in the rabbit have shown that the placental iodide transport is capable of generating a fetal serum–to–maternal serum iodide concentration ratio of 5 to 9:1.[3,4] This is not the case in human pregnancy, and cretinism is more likely in the neonates of women with large iodine-deficiency goiters.[4,5] The human placenta appears freely permeable to iodide, but whether this transfer is carrier mediated as is chloride or sulfate transfer is not clear[6] (Fig. 4–1).

The placenta imposes a relative barrier to the thyroid hormones and is impermeable to TSH, so the fetal hypothalamic-pituitary-thyroid system develops largely autonomous of the maternal system. There are large maternal-to-fetal gradients of total and free thyroxine (T_4) and triiodothyronine (T_3) across the placenta during most of gestation. Near term, the T_4 gradient gradually becomes fetal to maternal as fetal thyroid function matures. The placental barrier is due in part to the presence in placental tissue of an inner-ring iodothyronine monodeiodinase (MDI), which converts T_4 to inactive reverse T_3 and T_3 to diiodothyronine (T_2). Placental tissue also contains a type II outer-ring MDI capable of catalyzing conversion of T_4 to active T_3. However, significant amounts of maternal T_4 reach the fetus early as well as late in gestation. Significant fetal tissue T_4 levels have been documented before the advent of fetal thyroid hormone production, and low levels of fetal T_4 have been demonstrated in the athyroid human fetus at term.

The placenta is permeable to the thioureylene antithyroid drugs, and TRH crosses the placenta readily (see Fig. 4–1). However, little endogenous TRH is normally detected in adult peripheral blood due to the presence of TRH-degrading enzyme systems in the blood.[7,8] Although the sera of pregnant women contain somewhat lower levels of these enzymes than do sera of nonpregnant women, the nearly immeasurable levels of TRH in the maternal circulation have little effect on fetal thyroid function. The placenta synthesizes a pro-TRH molecule, and fetal gut tissues, particularly pancreas, produce TRH.[7] Both placental and pancreatic TRH have been isolated and characterized and found to be identical to hypothalamic TRH. The high circulating levels of TRH in fetal blood are due both to increased production in extrahypothalamic tissues and to low or absent levels of TRH-degrading activity in fetal blood. Human cord values of TRH are also elevated. The significance of the extrahypothalamic TRH in the fetus is not clear.

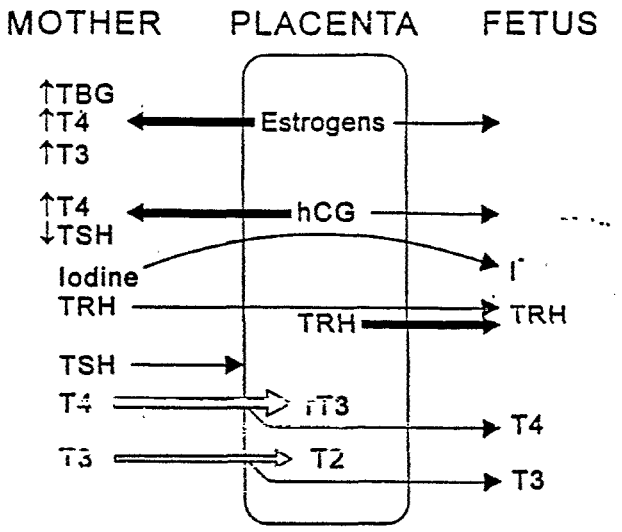

Figure 4–1 • Schematic representation of the role of the placenta in thyroid metabolism during human pregnancy. The placenta produces estrogens and a human chorionic gonadotropin (hCG), which increase maternal thyroxine-binding globulin (TBG) levels and stimulate maternal thyroid hormone production, respectively. Both activities tend to increase maternal thyroxine (T_4) and triiodothyronine (T_3) concentrations and inhibit maternal thyroid-stimulating hormone (TSH) secretion. Iodide and thyrotropin-releasing hormone (TRH) readily cross the placenta. In addition, the placenta synthesizes TRH. The placenta is impermeable to TSH and only partially permeable to T_4 and T_3. Placental type III iodothyronine monodeiodinase enzymes degrade T_4 to reverse T_3 and T_3 to 3,3′-diiodothyronine (T_2). The placenta also is permeable to the thiourea drugs used to treat maternal Graves disease.

In addition to TRH, the placenta produces thyrotropin-like activity.[4,9] The α-subunit of TSH is identical to that of human chorionic gonadotropin (hCG), and the β-subunit of hCG has structural homology with the β-subunit of TSH; thus, hCG has some TSH-like bioactivity. However, the biological potency of hCG is only approximately 0.01% that of TSH, and hCG normally has little influence on fetal thyroid system development or function. The large increase in maternal serum hCG activity that occurs early in pregnancy may account for the slight, transient suppression of maternal TSH levels seen early in the first trimester.

Thyroid System Maturation

Maturation of thyroid function in the fetus can be considered in three phases—hypothalamic, pituitary, and thyroidal.[1,10–14] Changes in these systems are complex and superimposed on the increasing production and increasing serum concentration of serum thyroid hormone–binding globulin (TBG) as well as the changing pattern of fetal tissue iodothyronine deiodination during gestation. As mentioned, the fetal thyroid

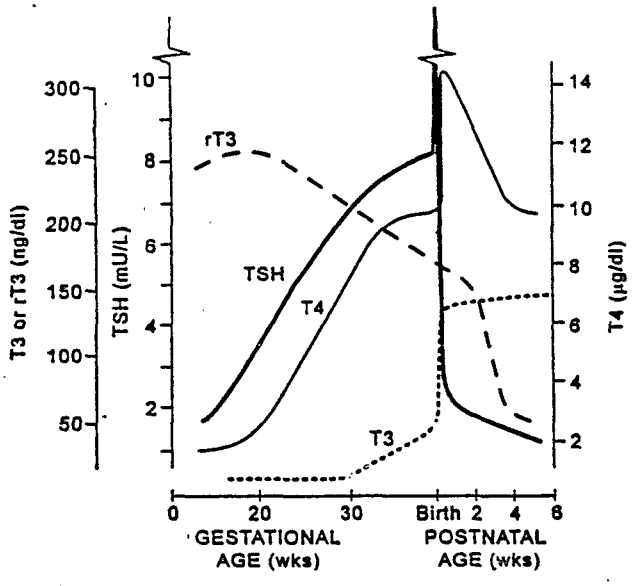

Figure 4–2 • Pattern of change in fetal and neonatal thyroid function parameters during pregnancy and extrauterine adaptation. The abrupt postnatal thyrotropin-stimulating hormone (TSH) surge reaches a peak of approximately 70 mU/L. (See text for details.) (Adapted with permission from Fisher DA: Endocrinology of fetal development. In Wilson JD, Foster DW (eds): *Textbook of Endocrinology*, 8th ed. Philadelphia, WB Saunders, 1992.)

gland is capable of iodide concentration and iodothyronine synthesis as early as 70 days of gestation. However, thyroid hormone production is limited until 18 to 20 weeks. At this time, thyroid follicular cell iodine uptake increases, and serum T_4 levels begin to increase (Fig. 4–2). Both total and free T_4 concentrations then increase steadily until the final weeks of pregnancy. The fetal serum T_3 concentration remains low (less than 15 ng/dl) until 30 weeks and then increases in two distinct phases: a prenatal phase and a postnatal phase. Prenatally, serum T_3 increases slowly after 30 weeks of gestation to reach a level of approximately 50 ng/dl (or 0.77 nmol/l) in term cord serum. Postnatally, both T_3 and T_4 serum concentrations increase twofold to sixfold within the first few hours of life, peaking at 24 to 36 hours after birth. These levels then gradually decline to levels characteristic of infancy over the first 4 to 5 weeks of life. The prenatal increase in serum T_3 appears to be in large part due to progressive maturation of hepatic type I (phenolic) outer-ring iodothyronine deiodinase activity and increasing hepatic conversion of T_4 to T_3, although other tissue sources of deiodinase, such as brown fat and kidney, may be involved.

Fetal serum TSH increases from a low level at 18 weeks to a peak level of approximately 10 mU/l at term. At the time of parturition, in response to neonatal (cold) extrauterine exposure there is an acute release of TSH (TSH surge), with blood levels peaking at a mean concentration of approximately 70 mU/L at 30 minutes. Circulating TSH levels remain modestly elevated for 2 to 3 days after birth. The increase in serum T_4 levels immediately after birth is TSH dependent. The increase in T_3 concentration is due in part to TSH stimulation of T_3 production and in part to further rapid maturation of tissue outer-ring MDI activity and T_4 to T_3 conversion in the neonatal period.

Fetal thyroid gland function develops under the influence of an increasing serum TSH level during the second half of gestation (Fig. 4–3). A parallel increase in serum free T_4 levels during the last trimester is associated with a progressive increase in the ratio of free T_4 to TSH concentration, suggesting changes in both the pituitary thyrotroph sensitivity to the negative feedback effect of thyroid hormones on TSH secretion during this period and the thyroid follicular cell sensitivity to TSH. A progressive maturation of the thyroidal response to TSH has been shown in the fetal sheep and seems likely in the human fetus. The events involved in maturation of the negative feedback control system are not yet clear; changes in pituitary thyrotroph T_3 and/or TRH receptors, a decrease in thyrotroph outer-ring iodothyronine deiodinase activity, and/or a decreasing nuclear T_3 receptor–mediated action on TSH biosynthesis might be involved.

The ontogeny of TRH secretion and function in the human fetus remains somewhat obscure. TRH production from the placenta and gut tissues and relatively high serum TRH levels have been demonstrated in the fetal sheep.[7] TRH immunoactivity is detectable in the human fetal pancreas

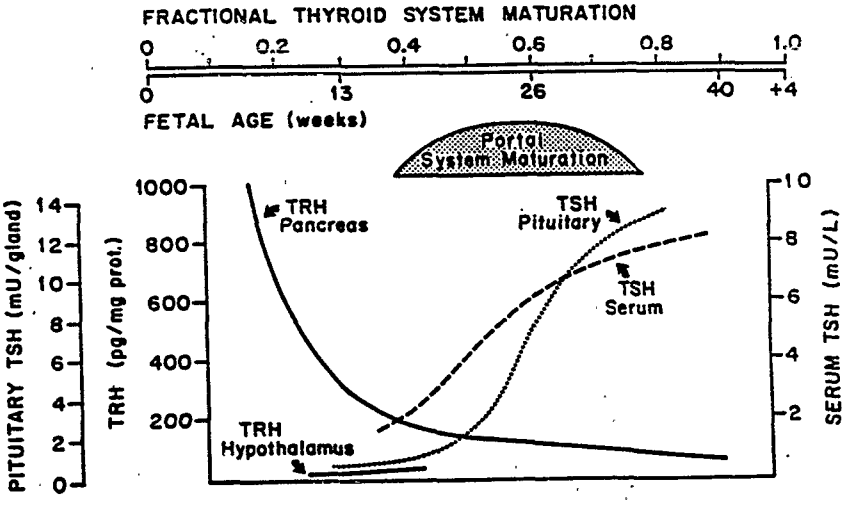

Figure 4–3 • Changes in fetal thyroid-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) levels in pancreas, hypothalamus, serum, and pituitary during human gestation. Hypothalamic TRH concentrations increase progressively after midgestation, but the pattern of change has not been documented in the human fetus. (Reproduced from Fisher DA, Polk DH: Development of the fetal thyroid system. In Thorburn GD, Harding R (eds): *Textbook of Fetal Physiology*. New York, Oxford University Press, 1994, by permission of Oxford University Press.)

early in gestation and in the hypothalamus by midgestation, increasing markedly in the third trimester after the peak in serum TSH activity is noted (see Fig. 4–3). Serum TRH levels in the human fetus are relatively high at term.[7] The premature infant (before 30 to 32 weeks) is characterized by low circulating levels of T_4 and free T_4, a normal or low level of TSH, and a normal or prolonged TSH response to TRH, indicating a state of physiological TRH deficiency. The full-term human fetus responds to pharmacological maternal doses of TRH with a somewhat prolonged increase in TSH, suggesting a degree of relative hypothalamic (tertiary) hypothyroidism. Peripheral sources of TRH (placenta and pancreas) contribute to the elevated circulating levels of fetal and cord blood TRH and may be responsible, in part, for stimulating TSH release in the fetus before the increase in hypothalamic TRH concentration.

In summary, the control of fetal thyroid hormone secretion can be characterized as a balance among increasing hypothalamic TRH secretion, increasing thyroid follicular cell sensitivity to TSH, and increasing pituitary sensitivity to thyroid hormone inhibition of TSH release. The fetus progresses from a state of both primary (thyroidal) and tertiary (hypothalamic) hypothyroidism in midgestation through a state of mild tertiary hypothyroidism during the final weeks of pregnancy to fully mature thyroid function in the perinatal period.

Maturation of Thyroid Hormone Metabolism

The thyroid gland is the sole source of T_4. Most of the circulating T_3 after birth is derived from conversion of T_4 to T_3 via monodeiodination in peripheral tissues. Deiodination of the iodothyronines is the major route of metabolism, and monodeiodination may occur either at the outer (phenolic) ring or the inner (tyrosyl) ring of the iodothyronine molecule (Fig. 4–4).[1, 4, 10, 14, 15] Outer-ring monodeiodination of T_4 produces T_3, the active form of thyroid hormone with greatest affinity for the thyroid nuclear receptor. Inner-ring monodeiodination of T_4 produces rT_3, an inactive metabolite. In mature humans, between 70% and 90% of circulating T_3 is derived from peripheral conversion of T_4, and 10% to 30% is derived from direct glandular secretion. Nearly all the circulating rT_3 is derived from peripheral conversion, with only 2% to 3% coming directly from the thyroid gland. T_3 and rT_3 are progressively metabolized to diiodinated, monoiodinated, and noniodinated forms of thyronine, none of which has biological activity.

Two types of outer-ring iodothyronine MDI have been described. Type I MDI, predominantly expressed in liver and kidney, is a high-K_m enzyme that is inhibited by propylthiouracil and stimulated by thyroid hormone. Type II MDI, predominantly located in brain and pituitary tissues and brown adipose tissue (BAT), is a low-K_m enzyme that is insensitive to propylthiouracil and inhibited by thyroid hormone. The type II enzyme also is present in placenta. Type I MDI activity in liver and, to a lesser extent, kidney and muscle accounts for most of the circulating T_3. The type I MDI also is capable of inner-ring monodeiodination, particularly of T_4 sulfate (to rT_3 sulfate) and T_3 sulfate (to T_2 sulfate). Type II 5′-MDI acts primarily to increase local intracellular levels of T_3 in the brain and pituitary tissues and BAT. An inner (tyrosyl) ring iodothyronine MDI (type III MDI) has been characterized in most fetal tissues, including the placenta. This enzyme system catalyzes the conversion of T_4 to rT_3 and T_3 to diiodothyronine.

Both type I and type II MDI are developmentally regulated and are present in third-trimester fetuses. In sheep, a species in which thyroid hormone system maturation closely resembles that in the human, hepatic type I MDI activity increases approximately 100% and brain type II MDI activity increases approximately 50% during the last third of gestation.[15] Both deiodinase species are thyroid hormone responsive. However, hepatic type I MDI activity becomes thyroid hormone responsive (i.e., activity decreases with hypothyroidism) only during the final weeks of gestation. Brain type II MDI is responsive (increases with hypothyroidism) throughout the final third of gestation. Thus, in the hypothyroid fetus, T_4 appears to be shunted from the liver to the brain, where it is preferentially deiodinated to T_3 to provide a source of intracellular T_3 to tissues (e.g., brain, pituitary) dependent on T_3 during fetal life. Type I enzyme activity (to provide increased serum T_3 levels) normally increases only during the final weeks of gestation and during postnatal life.

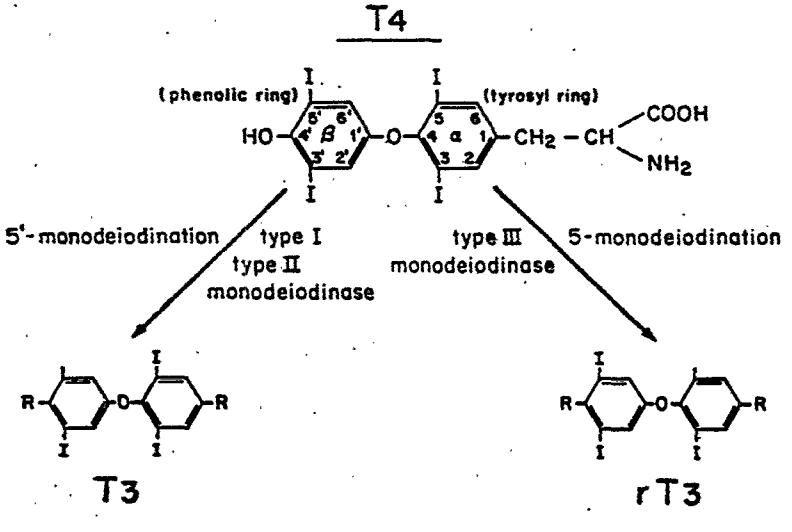

Figure 4–4 • Deiodination of thyroxine by type I, type II, and type III iodothyronine monodeiodinase enzymes. The type I enzyme also is capable of inner ring monodeiodination, particularly of the sulfated conjugates (not shown). (See text for details.)

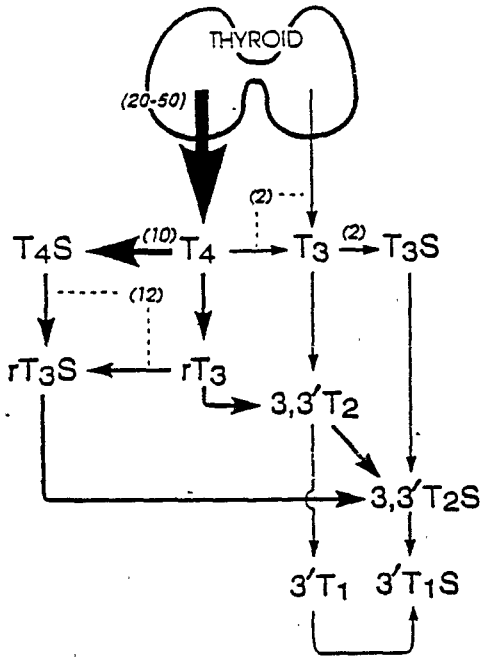

Figure 4–5 • Putative pattern of production and metabolism of iodothyronines in fetal sheep during the last third of gestation. Numbers in parentheses indicate production rates in micrograms per kilogram per day. (Reproduced with permission from Polk DH, Fisher DA, Wu SY: Alternate pathways of thyroid hormone in developing mammals. In Wu SY, Visser TJ (eds): *Thyroid Hormone Metabolism.* Boca Raton, CRC Press, 1994.)

Fetal thyroid hormone metabolism is characterized by a predominance of type III enzyme activity, particularly in liver, kidney, and placenta, accounting for the increased circulating levels of rT_3 observed in the fetus.[14, 15] However, the persistence of high circulating rT_3 levels for several weeks in the newborn indicates that type III MDI activities expressed in nonplacental tissues are most important to the maintenance of high circulating rT_3 levels. The mixture of type II and type III MDI activities in the placenta provides for the conversion of T_4 to T_3 and of T_4 and T_3 to rT_3 and T_2, respectively.

Sulfated iodothyronines are the major thyroid hormone metabolites circulating in the fetus.[14–16] Sulfokinase enzymes are present early in fetal life, and recent data suggest that sulfation of the phenolic hydroxyl group of the iodothyronine molecule may be a normal prerequisite step for monodeiodination.[17, 18] The sulfated iodothyronines are preferred substrates for type I MDI, and concentrations are high in fetal serum, in part because of low type I MDI activity. However, increased production of sulfated metabolites also is involved. In fetal sheep during the last third of gestation, the production rates of T_4, rT_3, T_3, T_4S, rT_3S, and T_3 sulfate are approximately 40, 5, 2, 10, 12, and 2 ng/kg/day, respectively (Fig. 4–5). The sulfate metabolites are biologically inactive, so the sum of biologically inactive iodothyronines produced daily by the fetal sheep ($T_4S + rT_3 + rT_3S + T_3S = 10 + 5 + 12 + 2$, or 29 ng/kg/day) accounts for the large majority of thyroid hormones produced in the euthyroid fetus. There is some evidence that T_3S has biological activity (suppresses TSH) in vivo, suggesting that it can be desulfated by one or more tissue sulfatase enzymes. Nevertheless, the low production rates and low levels of T_3 metabolites ($T_3 + T_3S = 2 + 2$, or 4 ng/kg/day) and the high ratio of inactive to active metabolites (29:4 ng/kg/day) suggest that fetal thyroid hormone metabolism is largely oriented to inactivating T_4, presumably to avoid tissue thermogenesis and potentiate the anabolic state of the rapidly growing third-trimester fetus. This is accomplished by early activation of type III MDI, inactivation of type I MDI, and augmented sulfation, probably in large part by liver tissue.

The presence of the type II MDI in brain tissue provides for preferential T_3 supply to this tissue, particularly in the event of T_4 deficiency, and helps ensure provision of T_3 during late gestation, when brain development is thyroid hormone dependent.[14, 19, 20] Whether early brain embryogenesis is thyroid hormone dependent is unclear at the present time, but before the advent of fetal thyroid function, the limited maternal-to-fetal T_4 transfer early in pregnancy may be important in this regard.

Both T_3 and T_4 in fetal blood are associated with various plasma proteins, including TBG, thyroxine-binding prealbumin (TBPA), and albumin.[21] TBG serves as the primary transport protein for both T_3 and T_4; approximately 70% of total T_4 and 40% to 60% of total T_3 are bound to TBG. The remainder of the thyroid hormones are distributed approximately equally between TBPA and albumin. The binding affinities of these proteins are such that adult free T_4 and T_3 concentrations are approximately 0.03% and 0.3%, respectively, of total hormone concentrations. TBG, TBPA, and albumin are produced by the liver, and production of these proteins increases progressively during the second half of gestation. Fetal hepatic TBG production is stimulated by estrogen, and hepatic clearance of TBG is reduced secondary to an estrogen-induced increase in sialylation of TBG. The increasing placental estrogen production during pregnancy accounts in large part for the progressive increase in fetal total T_4 levels between midgestation and 34 to 35 weeks of gestation. However, the free T_4 level also increases due to progressively increasing T_4 production, which exceeds the rate of increase of TBG levels.

Extrauterine Thyroid Adaptation

At the time of parturition, the neonate must rapidly convert from the fetal state of thyroid hormone inactivation to a state of relative thyroidal hyperactivity.[1, 10] During the first hours after birth, there is an abrupt twofold to sixfold increase in circulating T_4 and T_3 levels, respectively (see Fig. 4–2). This is due to the abrupt increase in pituitary TSH secretion, stimulating increased hormone secretion from the thyroid gland. The cold-stimulated TSH surge is short lived, and the decrease in TSH that follows during the 72 to 96 hours after birth is due to feedback inhibition by the elevated serum T_4 at either the hypothalamic or pituitary level (or both). Serum T_3 levels increase both in response to the TSH surge and secondary to increased tissue type I MDI activities, which maintain the high serum T_3 levels characteristic of extrauterine life after the TSH levels fall. The type II MDI activity in BAT increases during the last weeks of gestation to potentiate catecholamine-stimulated BAT thermogenesis to maintain body temperature during the neonatal period.

Figure 4–6 is a summary of the changes in the ratios

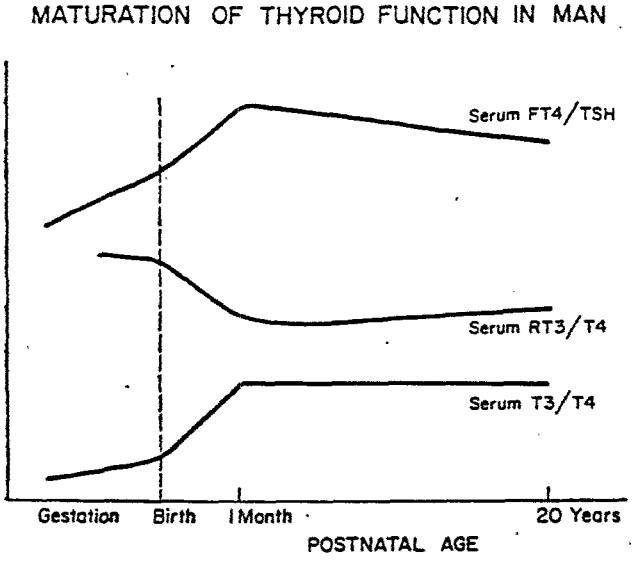

Figure 4–6 • Maturation of the free thyroxine (FT_4) to thyroid-stimulating hormone (TSH) ratio and the ratios of triiodothyronine (T_3) and reverse T_3, (rT_3) to thyroxine (T_4) in the human fetus, children, and adolescents. (See text for details.)

of serum free T_4 (FT_4) to TSH, of serum reverse T_3 (RT_3) to T_4, and of serum T_3 to T_4 during the period of late intrauterine and postnatal thyroid system development. The free T_4-to-TSH ratio change reflects the maturation of hypothalamic-pituitary-thyroid control, which is largely complete by 1 month of postnatal life in the normal human newborn. The perinatal changes in the RT_3 and T_3-to-T_4 ratios reflect maturational changes in the iodothyronine MDI enzyme systems from the fetal to the postnatal state. The transition from predominant type III MDI activity to type I MDI activity is clear.

The ontogenesis of a variety of thyroid actions has been characterized in rodents and sheep; these include tissue thermogenesis, carcass and muscle growth, skeletal maturation, skin and brain maturation, and hormone and growth factor production and action. Some of these effects represent thyroid hormone actions on specific gene products, probably mediated via thyroid hormone receptor control of gene transcription. Other thyroid hormone actions represent complex events, the mechanisms of which are not yet understood, such as the effects on growth, skeletal maturation, and brain development. In humans, thyroid nuclear receptors have been reported in fetal lung, brain, heart, and liver at 13 to 19 weeks of gestation. The most prominent thyroid hormone actions that have been characterized in the fetus are the effects of hypothyroidism on serum TSH and bone maturation. Most of the other effects of thyroid hormones on perinatal developmental processes occur postnatally.

Thyroid Dysfunction Syndromes in the Premature Infant

Transient Hypothyroxinemia

Serum T_4 concentrations increase progressively with gestational age, so most term infants have serum T_4 concentrations of more than 6.5 μg/dL. Only 2% to 3% have serum T_4 levels below this level.[22] In contrast, approximately 50% of premature infants delivered before 30 weeks of gestation have serum T_4 values of less than 6.5 μg/dL. Infants with hypothyroxinemia also have relatively low levels of free T_4. These levels are not in the low range for neonates with congenital hypothyroidism; rather, they are similar to levels for adults. The relatively low free T_4 levels in premature infants are associated with normal or even low basal serum TSH values and normal TSH and T_4 responses to TRH, the latter indicating responsive pituitary and thyroid glands. The hypothyroxinemia is transient, correcting spontaneously (over 6 to 10 weeks) with progressive maturation. Postnatal growth and development of these infants are normal. Thus, such infants appear to manifest a state of hypothalamic (or tertiary) hypothyroidism or immaturity that represents a normal stage of thyroid system development. Transient hypothyroxinemia corrects spontaneously as the infants mature in the extrauterine environment.[22, 23] Therapy does not appear necessary unless the serum TSH level is elevated.

Transient Primary Hypothyroidism

Transient hypothyroidism in the neonate, as characterized by low serum T_4 and high TSH concentrations, is more common in Europe than in America, and the prevalence varies geographically relative to iodine intake.[23–25] Transient hypothyroidism in Belgium occurs in approximately 20% of premature infants, and the prevalence is higher with decreasing gestational age. Cord blood T_4 and TSH values in these infants usually are in the normal range for premature infants. Premature infants require higher iodine intake levels than term infants to maintain a positive iodine balance and adequate T_4 production in the extrauterine environment, and in iodine-deficient geographical areas they may develop neonatal iodine deficiency. The primary hypothyroid state develops during the first 1 to 2 weeks of extrauterine life and often is superimposed on the transient hypothyroxinemia characteristic of prematurity. Urinary iodine and thyroid iodine concentrations are reduced. The hypothyroidism is transient but may persist for 2 to 3 months, so treatment is recommended; T_4 or T_3 can be prescribed. The average time to recovery of function and discontinuation of treatment in Belgium was 2 months. Iodine treatment also corrects the primary hypothyroid state in such infants.

Transient Idiopathic Hyperthyrotropinemia

Idiopathic hyperthyrotropinemia is a rare disorder. The serum TSH concentration is increased, often markedly, but other thyroid function parameters are normal, and the infants are euthyroid.[26–28] Transient neonatal hyperthyrotropinemia is a relatively frequent phenomenon in Japan, where it is detected in approximately 1 in 18,000 newborns.[27] In a recent report of 16 patients followed for 2 to 7 years the elevated serum TSH levels at 2 to 7 weeks of age ranged from 17 to 77 mU/L (17 to 77 μU/mL). Serum T_4, T_3, and free T_4 levels were normal, as were basal metabolic rates and thyroid radioiodine uptake values. All infants had increased TSH responses to exogenous TRH, whereas none

had detectable levels of TSH receptor–blocking antibodies (TBA). The elevated TSH values spontaneously normalized in 11 of the 16 infants within 6 months, excluding an abnormal TSH molecule or a TSH receptor defect. However, the augmented TSH response to TRH persisted for 3 to 7 years in children. All infants also had a normal T_3 response to TSH, which tends to exclude a hormone synthetic defect; however, small diffuse goiters developed in 3 of 16 patients by 5 to 7 years. The mechanism for the hyperthyrotropinemia remains obscure. With normal serum T_4 and free T_4 levels, normal thyroid scan results, and absent TBA, many such infants are followed expectantly.[28] It is always necessary to rule out primary thyroid disease in such patients. If treatment is instituted, the criteria for management are as described for other infants with congenital hypothyroidism (CH).

Low-T_3 Syndrome

In the preterm infant, the changes in thyroid function parameters during neonatal adaptation are qualitatively similar to those in term infants but are quantitatively obtunded.[23, 26, 29] The neonatal TSH surge and the neonatal T_4 peak decrease in amplitude with decreasing gestational age; the neonatal T_3 peak also is obtunded. This transient low-T_3 state probably is related to the state of relative undernutrition during the neonatal period. Premature infants have an increased susceptibility to neonatal morbidity, including respiratory distress, and they have an increased risk of birth trauma, vascular accidents, hypoxia, hypoglycemia, hypocalcemia, and infection superimposed on relative malnutrition. All of these factors tend to inhibit T_4 to T_3 conversion in the neonatal period and aggravate the extent of the low-T_3 state characteristic of prematurity. Serum T_3 values may remain low in these infants for 1 to 2 months.

Features of the low-T_3 syndrome in premature infants include a low serum T_3 concentration secondary to a decreased rate of conversion of T_4 to T_3, variable but usually elevated serum rT_3 levels, and normal or low total serum T_4 concentrations. Free T_4 levels are in the range of values for healthy premature infants of matched gestational age and weight. In some infants, serum TBG levels are low, and there may be an inhibitor of T_4 binding to TBG as described in adults with the low-T_3 syndrome.[30] Serum TSH concentrations are normal, indicating a euthyroid state.

Congenital Hypothyroidism

Newborn Screening

Newborn screening for CH is now routine in most industrialized societies.[31–33] Due to screening and early diagnosis, treatment of affected infants usually is initiated within 45 days of birth, and IQ levels in treated infants measured at 5 to 7 years of age have been normal. Newborn CH screening tests are usually carried out with dried blood spot samples collected via skin puncture. In North America, T_4 is measured initially, and TSH is measured in samples with the lowest 10% to 20% of T_4 results. In other areas of the world, direct TSH screening has commonly been used. In effect, all neonatal thyroid screening programs include screening for elevated serum TSH concentration as the most reliable indicator of primary hypothyroidism. The threshold value for a significant TSH elevation in most screening programs is 20 to 25 mU/L (20 to 25 μU/mL). The preferred time for blood sampling is 3 to 5 days after birth. However, many mother-newborn diads are now discharged from the hospital within 3 days of delivery, and some are discharged within 1 day. Early measurement increases the prevalence of infants demonstrating a modest elevation of blood spot TSH concentrations due to the physiological neonatal TSH surge; thus, early screening for CH increases the number of false-positive results. In most programs, the ratio of false-positive to confirmed CH case is 2 to 3:1. The effect of early hospital discharge of mother and infant in one study increased this ratio from 2.5:1 to approximately 5:1. The ratio will vary, however, depending on the threshold value established for a significant TSH elevation by the individual program. Some programs have a higher threshold value for infants discharged on day 1. The prevalence of CH approximates 1 in 4000 births.[31–35] Etiologies include thyroid dysgenesis (e.g., aplasia, hypoplasia, ectopy), thyroid dyshormonogenesis, hypothalamic-pituitary (TSH) deficiency, and transient hypothyroidism (usually iodine, drug, or maternal antibody induced); the proportions approximate 75%, 10%, 5%, and 10%, respectively, of all cases of CH (Table 4–1).

Thyroid Dysgenesis

The term *thyroid dysgenesis* describes infants with ectopic or hypoplastic thyroid glands (or both) as well as those with total thyroid agenesis. Thyroid dysgenesis is the etiological factor in most infants with permanent CH detected in newborn screening programs.[31–35] Some thyroid tissue probably is present in two thirds of these infants, so they represent a spectrum of severity of thyroid deficiency. A normal or near-

Table 4–1 Thyroid Disorders and Their Approximate Prevalences in the Neonatal Period

Thyroid Dysgenesis	1:4000
Agenesis	
Hypogenesis	
Ectopia	
Thyroid Dyshormonogenesis	1:30,000
TSH unresponsiveness	
Iodide trapping defect	
Organification defect	
Defect in thyroglobulin	
Iodotyrosine deiodinase deficiency	
Hypothalamic-Pituitary Hypothyroidism	1:100,000
Hypothalamic-pituitary anomaly	
Panhypopituitarism	
Isolated TSH deficiency	
Thyroid hormone resistance	
Transient Hypothyroidism	1:40,000
Drug induced	
Maternal antibody induced	
Idiopathic	

normal circulating level of T_3 in the presence of low T_4 suggests the presence of residual thyroid tissue, and this can be confirmed by a thyroid scan. A measurable level of serum thyroglobulin (Tg) indicates the presence of some thyroid tissue; athyroid infants have no circulating Tg.

Thyroid dysgenesis is more prevalent in female infants than in male infants; the female-to-male ratio approximates 2:1. The disorder has been reported to be less prevalent in black infants (1:32,000) than in white infants and is more frequent (1:2000) in Hispanic infants. Although thyroid dysgenesis usually is sporadic, rare familial cases have been described, and the prevalence is increased in infants with Down syndrome. An increased prevalence of nonthyroid anomalies has been reported in infants with CH, and a seasonal variation in incidence has been observed in Japan and Australia.[34–36] In rare instances, thyroid dysgenesis has occurred in association with maternal autoimmune thyroiditis. However, this appears to be coincidental; there is no correlation between thyroid dysgenesis and the presence of maternal autoimmune thyroiditis or circulating thyroid antimicrosomal or antithyroglobulin autoantibodies.[34]

Inborn Defects of Thyroid Hormone Metabolism

General Features

The function of the thyroid gland is to concentrate iodide from the blood and return it to peripheral tissues in a hormonally active form. The major substrates for thyroid hormone synthesis are iodide and tyrosine. Tyrosine is not rate limiting, even in individuals with phenylketonuria, in whom tyrosine becomes an essential amino acid. Iodine, in contrast, is a trace element that can be rate limiting in thyroid hormone synthesis. The process of thyroid hormone biosynthesis is stimulated by TSH binding to the follicular cell TSH receptor and cyclic AMP (cAMP) activation. Processes stimulated by cAMP include cell membrane iodide transport, Tg synthesis, oxidation and organification of trapped iodide, activation of colloid endocytosis and intracellular phagolysosome formation, hydrolysis of Tg to release the iodotyrosine (monoiodotyrosine [MIT] and diiodotyrosine [DIT]) and iodothyronine (T_4 and T_3) residues, deiodination of MIT and DIT by an iodotyrosine deiodinase, and release of the T_4 and T_3 into the circulation. Significant amounts of Tg also escape from the gland, predominantly via the thyroid lymphatic system. These events are summarized in Figure 4–7. Infants with defects in thyroid hormone metabolism account for approximately 10% of newborns with CH. A defect in TSH binding and action and several functional abnormalities have been described[37, 38]; these involve decreased iodide trapping, defective organification of trapped iodide, abnormalities of Tg structure, and deficiency of iodotyrosine deiodination and recycling. These disorders usually are transmitted as autosomal recessive traits. Except for the familial incidence and tendency for affected individuals to develop goiter, the clinical manifestations of CH due to a biochemical defect are similar to those in infants with thyroid dysgenesis. Thyroid enlargement may be manifest at birth, but in many patients development of the goiter is delayed. Features of these disorders are summarized in Table 4–2.

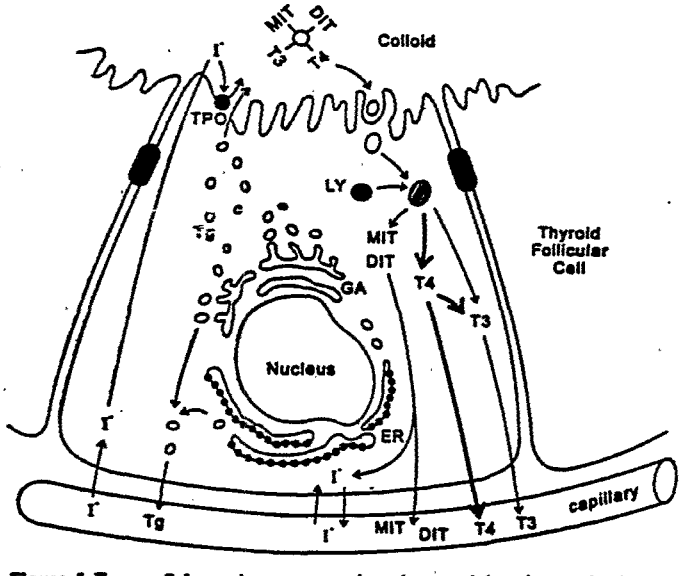

Figure 4–7 • Schematic representation characterizing the synthesis and secretion of thyroid hormones by the thyroid follicular cell. TPO, thyroid peroxidase enzyme; Tg, thyroglobulin; Ly, lysosome; the hatched inclusion is the phagolysosome; GA, Golgi apparatus; ER, rough endoplasmic reticulum.

TSH Unresponsiveness

The thyroid follicular cell response to TSH involves a series of coordinated steps, including TSH binding to a receptor in the plasma membrane, activation of adenyl cyclase, synthesis of cAMP, activation of protein kinase(s), phosphorylation of receptor protein(s), and stimulation of the several intracellular events of thyroid hormone synthesis and release. A defect at one of several sites could lead to an abnormality in thyroid responsiveness to TSH. Only a few patients with TSH nonresponsiveness have been reported; characteristically, they present with neonatal CH, including low serum T_4 and increased TSH concentrations.[37, 38] Thyroid radioiodine uptake is low or low-normal and unresponsive to TSH. A 19-year-old hypothyroid patient without a goiter but with high levels of bioactive TSH and radioiodine uptake unresponsive to TSH has been reported, indicating that mild defects may occur.

Failure to Concentrate Iodide

The transport of iodide across the thyroid follicular cell membrane from plasma to cytosol is the first step in thyroid hormone biosynthesis. Under normal circumstances, the thyroid cell membrane iodide pump generates a thyroid-to-serum concentration gradient in excess of 20 to 30/1; this gradient can reach several hundredfold when the thyroid gland is stimulated by a low-iodine diet, by TSH, by a variety of thyroid-stimulating immunoglobulins in Graves disease, or by drugs that impair the efficiency of hormone synthesis. Other tissues, such as the salivary glands, gastric mucosa, mammary glands, ciliary body, choroid plexus, and

Table 4–2 | Inborn Abnormalities of Thyroid Hormone Metabolism

Abnormality	Prevalence	Inheritance	Clinical Features							Molecular Abnormality
			CH	Goiter	T_4	TSH	Tg	RAIU	Other	
Familial TSH deficiency	Rare	AR	Yes	No	↓	↓	↓	↓	Absent TSH response to TRH	*TSH*β gene mutations
Pit-1 deficiency hypopituitarism	Not yet clear	AR	Yes	No	↓	N or ↓	↓	↓	GH and PRL deficiencies	*Pit-1* gene mutations
TSH unresponsiveness	Rare	AR	Yes	No	↓	↑	↓	N	No RAIU, T_4, or Tg response to TSH	TSH receptor gene mutations
Iodide transport defect	Rare	AR	Yes	Yes	↓	↑	↑	↓	Salivary and gastric tissues also fail to concentrate iodide; hypothyroid state responds to iodide therapy	Defect not characterized
Organification defects	1:40,000 newborns	AR	Yes	Yes	↓	↑	↑	↑	Positive perchlorate discharge test	Thyroid peroxidase gene mutations; defective H_2O_2 generation
Pendred syndrome	1:50,000 children	AR	V	Yes	N, ↑	↑	↑	↑	Deaf mutism; positive perchlorate discharge	Thyroid defect not clear; cochlear defect
Tg defects	1:40,000 newborns	AR	Yes	Yes	↓	↑	↓ ↑	↑	Usually low Tg with no Tg response to TSH	Tg gene mutations (absent or defective Tg); hyposialylated Tg due to sialyltransferase defect
Iodotyrosine deiodinase defect	Rare	AR	Yes	Yes	↓	↑	↑	↑	High RAIU with early discharge; high serum MIT, DIT; failure to deiodinate IV dose of labeled DIT (excretion intact)	Presumed iodotyrosine deiodinase gene mutation
Thyroid hormone resistance	1:100,000 newborns?	Autosomal dominant or sporadic	V	Yes	↑	N, ↑	↑	↑	Generalized resistance, TSH N or ↑, peripheral resistance; TSH ↑; pituitary resistance TSH ↑ (patient hyperthyroidic)	Thyroid nuclear receptor gene mutations (TRβ; TRα)
Autosomal dominant hyperthyroidism	Rare	Autosomal dominant	No hyperthyroid	Yes	↑	↓	↑	↑	Absence of thyroid autoimmunity	Activating TSH receptor gene mutations

AR, autosomal recessive; RAIU, thyroid radioactive iodine uptake; T_4 and TSH refer to serum concentrations, V, variable.

placenta, are also capable of concentrating iodide against a gradient. However, these tissues are not capable of organifying inorganic iodide.

TSH stimulates iodide transport through a sequence of increased cAMP formation and RNA and protein synthesis. Certain anions that are accumulated by the thyroid are capable of competitively inhibiting iodide transport; these, in order of increasing potency, include bromide, nitrite, thiocyanate, selenocyanate, fluoroborate, and perchlorate. Thiocyanate and perchlorate have been used clinically to block iodide transport.

Several patients have been described with hyperplastic thyroid glands but only minimal uptake of radioactive iodide at 24 hours.[37, 38] The thyroid glands in these patients are enlarged, and the patients usually manifest CH. Other iodine-concentrating tissues (e.g., salivary glands, gastric mucosa) also fail to concentrate iodide from the circulation. Lugol solution ameliorates the hypothyroidism by increasing the serum iodide to high levels and increasing the intrathyroidal inorganic iodide concentration via diffusion. The molecular defect in this disorder is not known.

Several patients also have been reported with a partial defect in iodide trapping manifest in thyroid, salivary, and gastric tissues. Thyroid radioiodine uptake was decreased but not absent in these patients and did not respond to TSH. The salivary-to-plasma ratio of radioiodine also was reduced but not entirely absent. Nevertheless, the patients were hypothyroid with mental retardation.

Peroxidase System Defects (Organification Defects)

Normally, iodide concentrated by the thyroid follicular cell is rapidly oxidized and bound in organic form. Organification of iodide involves two processes: oxidation of iodide and iodination of Tg-bound tyrosine. Trapped iodide is oxidized to an active intermediate followed by iodination of Tg-bound tyrosyl residues to form the iodotyrosines MIT and DIT. Two DIT residues are coupled to form T_4, and MIT and DIT couple to form T_3. Both tyrosyl iodination and coupling are catalyzed by a thyroid peroxidase (TPO) enzyme system. TPO is a membrane-bound heme protein that requires peroxide and an acceptor, which in the normal thyroid gland is Tg but can be albumin or other proteins or peptides. The hydrogen peroxide may be provided by one or more of several flavoprotein enzyme systems.

By 1992, defective organification of iodide had been reported in approximately 120 patients.[37–40] The defects included a quantitative deficiency of TPO; a TPO gene mutation leading to a structurally abnormal, functionally defective TPO molecule; or a deficiency in hydrogen peroxide generation. The complete defect can be detected with a perchlorate discharge test. Perchlorate is administered 1 to 2 hours after a dose of radioiodine. If organification is impaired, there is a rapid and profound discharge of the thyroidal radioiodine trapped during the following 1- to 2-hour period. Patients with abnormal TPO have a partial discharge. The test is not specific, however, and more definitive testing is necessary

for a precise diagnosis. The gene for TPO has been cloned and characterized, and disease-specific polymorphisms have been identified in several families.

The *Pendred syndrome,* which includes familial goiter and congenital eighth nerve deafness, is transmitted as an autosomal recessive trait.[37, 38] Approximately 750 cases had been reported in approximately 400 families by 1992; according to a survey in England, about 6% of deaf mute children were found to be affected.[37] The degree of impaired organification is mild to moderate and variable. Infants with the syndrome usually are not detected unless they are living in an iodine-deficient environment. Goiter often is delayed until middle or late childhood; goitrous children manifest a positive perchlorate discharge test, but TPO activity is normal. The defect is not yet clear.

Defects in Tg Synthesis

Tg is an essential substrate for organification and is the major protein component of thyroid colloid. It is an iodinated glycoprotein with a molecular weight approximating 650,000 Da and a sedimentation coefficient of 19.7 (19S). It is composed of two monomeric chains that are 2767 amino acids long; each has 67 tyrosine residues and 20 potential glycosylation sites. Approximately one third of the tyrosine residues are spatially oriented so they are susceptible to iodination. The Tg gene is located on chromosome 8. Genetic defects can lead to Tg deficiency or structural or functional abnormalities of the protein. Goiter and hypothyroidism usually are manifest at birth, but mild defects are likely to be described in association with later onset. Functional defects have included defective Tg transport with carbohydrate-deficient Tg sequestered in cytoplasmic membranes, deficient tyrosine residues or tyrosine residues buried within the molecule and not available for iodination, and sialic acid–deficient Tg (due to a sialyltransferase deficiency) containing MIT and DIT but defective coupling.[37, 38, 41, 42]

Iodotyrosine Deiodinase Defect

Deficiency of the iodotyrosine deiodinase can cause either CH or a less severe form of familial goiter. Failure to deiodinate thyroid MIT and DIT as they are released from Tg leads to severe iodine wastage because the nondeiodinated MIT and DIT leak out of the thyroid and are excreted in urine. Iodotyrosine deiodinases are present in both thyroid cells and peripheral tissues, and abnormalities involving both systems have been described.

The patients originally described were cretinous and hypothyroid with goiters presenting at birth or shortly thereafter. They manifested early, rapid thyroid radioiodine uptake and rapid spontaneous discharge; by 48 hours most of the thyroidal radioiodine was discharged.[37, 38] The serum in such patients contains high concentrations of iodotyrosines. They excrete essentially all of an intravenous dose of labeled iodotyrosine directly into urine, whereas normal subjects excrete the label almost entirely as free iodide. Partial defects have been described in both thyroid and peripheral tissues, in peripheral tissues only, and in thyroid tissue only. In patients with a mild defect, compensation may be possible in a high-iodine environment; a goiter may appear only if iodine intake is limited.

Thyroid Hormone Resistance

Patients with thyroid hormone resistance classically present with increased circulating levels of T_4 and T_3 with a normal or increased serum TSH concentration.[43, 44] Such infants may be detected in newborn-screening programs where TSH is measured directly. TSH levels are mildly to moderately increased, but the increased T_4 level would prevent detection in a primary T_4–secondary TSH screening program. The prevalence is not yet clear; more than 400 patients have been reported. Preliminary data from regional screening programs suggest a prevalence approximating 1 in 100,000 newborns. They have been classified into three phenotypes: generalized resistance to thyroid hormones (GRTH), pituitary resistance to thyroid hormone (PitRTH), and peripheral resistance to thyroid hormone (PRTH). Inheritance has been autosomal dominant in all familial cases except one. From 15% to 20% of cases appear sporadically.

Thyroid hormone action is mediated via nuclear thyroid hormone receptor (TR) proteins with zinc finger DNA-binding regions and thyroid hormone–binding domains. The latter have a 10:1 relative binding affinity for T_3 versus T_4. The TRs act as DNA transactivating factors to stimulate or suppress responsive genes. Two genes coding for the TR proteins have been described: an α gene on chromosome 17 and a β gene on chromosome 3. Each codes for several proteins via alternative splicing of the initial mRNA transcripts. There are at least two TRβ receptors ($TR\beta_1$ and $TR\beta_2$) and three TRα receptors ($TR\alpha_1$, $TR\alpha_{2\text{-}v1}$, and $TR\alpha_{2\text{-}v2}$). The $TR\alpha_2$ receptors do not bind T_3 but have functional DNA-binding domains. The $TR\beta_1$ mRNA is distributed in highest concentrations in brain, liver, kidney, and heart. $TR\beta_2$ mRNA is restricted to pituitary and brain tissues. $TR\alpha_1$ and $TR\alpha_2$ mRNA are widely distributed among tissues.

The molecular defect in all cases studied to date has involved the *TRβ*$_1$ gene on chromosome 3. In most affected subjects, specific *TRβ* gene mutations have been demonstrated, and most have been single amino acid deletions or substitutions involving the hormone-binding domain at the carboxy terminal end of the receptor molecule. There has been considerable variation of thyroid effects among tissues within family members with identical *TRβ* mutations.[44–48] TRs, like other steroid hormone superfamily receptors, bind to DNA response elements as monomers, homodimers, or heterodimers, and heterodimerization can involve another TR, including the $TR\alpha_2$ receptors, or other transactivation factors. The ability of the defective receptor to bind T_3, to bind to another TR, or to bind to other factors appears to determine the effect of the defective receptor in a given tissue. Affected members of most families studied have one normal and one abnormal *TRβ* allele. The abnormal *TRβ* with minimal or reduced T_3 binding fails to mediate T_3-regulated transcription and may block the action of the normal allele. This has been referred to as a dominant negative effect, presumably mediated by binding of the defective allele with normal *TRβ*, producing an inactive homodimer.

Recent studies of patients with the PitRTH phenotype

have revealed point mutations and decreased T_3 binding of $TR\beta_1$ receptors, similar to defects described for GRTH patients.[49, 50] These observations suggest that the apparent selective PitRTH and GRTH phenotypes are not qualitatively different syndromes but rather reflect a continuous spectrum of a similar molecular defect with variable tissue resistance.

Hypothalamic-Pituitary Hypothyroidism

Infants with organic TSH deficiency are relatively uncommon, with a prevalence in the range of 1:50,000 to 1:150,000 newborns.[26, 34, 51] These infants are not usually detected in newborn thyroid screening programs because all programs are designed to screen for hyperthyrotropinemia. However, some programs that use initial T_4 measurements to reduce the number of TSH specimens to be assayed report T_4 values and report infants with low blood spot T_4 and low (less than 20 to 25 mU/L) TSH levels. Most of such infants are premature infants manifesting transient hypothyroxinemia of prematurity. Organic hypothalamic-pituitary hypothyroidism can result from anomalous hypothalamic and/or pituitary development, functional panhypopituitarism, or isolated TSH deficiency; familial pituitary aplasia, familial absence of the sella turcica, familial panhypopituitarism, and familial TSH deficiency have also been described.

Familial isolated TSH deficiency is a rare disorder that is best characterized in Japanese patients. Several families have been reported with an autosomal recessive pattern of inheritance of nongoitrous CH.[52, 53] Serum T_4 and TSH concentrations are low, whereas other pituitary functions are intact. The thyroid gland responds to TSH; there is no TSH response to TRH. In one family recently studied, a single base substitution in the CAGYC region of the TSH β-subunit gene was identified. The mutated β-subunit mRNA coded for an altered β-polypeptide, which did not associate with TSH α-subunits to form active TSH. Recent studies have characterized at least four different *Pit-1* gene mutations associated with a subtype of panhypopituitarism manifesting growth hormone (GH), prolactin, and TSH deficiencies.[37, 54, 55] All were single base substitutions blocking *Pit-1* synthesis or function.

All of these disorders are characterized by a low serum T_4 concentration with a low or normal TSH level. Measurement of a low free T_4 concentration excludes a TBG-deficiency state as the cause of hypothyroxinemia. If TSH deficiency is suspected, measurements of serum cortisol and GH concentrations may indicate panhypopituitarism. Hypoglycemia in a term neonate suggests ACTH or GH deficiency or both. A computed axial tomography or nuclear magnetic resonance scan is useful in characterizing hypothalamic-pituitary anomalies. A subnormal serum TSH response (measured at 30 minutes) to infusion of 7 μg/kg TRH confirms a diagnosis of pituitary TSH deficiency. Selective studies measuring the TSH and TSH subunits can help characterize a thyrotropin gene defect. Therapy of the hypothyroidism in these infants is similar to therapy of other CH states. In addition, replacement of other pituitary or end organ hormone deficiencies is necessary.

Transient Hypothyroidism

Transient CH occurs in 5% to 10% of infants with CH detected in newborn thyroid screening programs. These infants manifest low or normal T_4 levels with variably elevated serum TSH values. The most common causes in North America are goitrogenic agents and transplacentally derived TSH receptor–blocking maternal autoantibodies. Autoantibody-mediated CH accounts for 1% to 2% of cases.[56] In areas of endemic iodine deficiency, transient CH (due to iodine deficiency) is more frequent.[57] Maternal iodine, antithyroid drug, or dietary goitrogen ingestion should be considered in all cases of CH. The presence of a goiter in the infant is supportive evidence of drug- or goitrogen-induced transient hypothyroidism. The thyroid scan result varies depending on the cause; iodine usually inhibits technetium or radioiodine uptake, whereas drug or dietary goitrogens typically increase uptake and produce a positive scan. Maternal TSH receptor–blocking antibody–induced hypothyroidism should be suspected in any case in which the mother has a history of autoimmune thyroid disease.[58–60] The presence in maternal or neonatal blood of a high level of TSH receptor–blocking antibody is strong supportive evidence. The transient CH in these infants is usually of short duration (1 to 2 weeks) in the case of drugs or of longer duration (1 to 4 months) if related to maternal blocking antibody, the half-life of which approximates 2 weeks. If the CH state persists beyond 2 weeks, treatment is in order. Feedback control of TSH is normal in these infants, and the serum TSH level is easily suppressed. Measurements of TSH receptor antibody levels can been conducted to determine when to discontinue therapy in TBA-mediated CH.

Evaluation of Infants with Presumptive Positive Screening Results

A positive screening report for CH in a newborn demands prompt evaluation of the infant, including a history, physical examination, and laboratory testing.[61–63] A history of autoimmune thyroid disease in the family suggests the possibility of transient CH, either drug or maternal TSH receptor autoantibody induced. Recurrent CH in the same sibship also suggests maternal autoantibody-mediated disease.[56] A history of familial congenital thyroid disease suggests thyroid dyshormonogenesis, which is usually transmitted as an autosomal recessive trait.

Physical examination may reveal one of several early and subtle manifestations of hypothyroidism, including a large posterior fontanelle (more than 1 cm in diameter), prolonged jaundice (hyperbilirubinemia for more than 7 days), macroglossia, hoarse cry, distended abdomen, umbilical hernia, hypotonia, or goiter.[61, 63] Fewer than 5% of infants are diagnosed on clinical grounds before the screening report, but 15% to 20% of infants have suggestive signs when carefully examined at age 4 to 6 weeks, after the screening results have been reported.

The diagnosis of CH is confirmed through serum measurements of T_4 and TSH concentrations.[61] In the neonatal period (1 to 4 weeks), serum T_4 and TSH levels of less than 84 nmol/L (6.5 μg/dL) and more than 10 mU/L (10 μU/mL), respectively, suggest CH. In infants with proved CH,

90% have TSH levels of more than 50 mU/L and 75% have T_4 concentrations of less than 84 nmol/L. Perhaps 20% of CH infants have T_4 levels in the range of 84 to 165 nmol/L (6.5 to 13 μ/dL), usually with clearly elevated TSH concentrations (more than 30 mU/L). A few infants manifest serum levels of T_4 in the low-normal range (84 to 165 nmol/L) with only modest TSH elevations (10 to 30 mU/L). Such infants may require repeat examinations to establish a diagnosis of CH. Serum T_3 or rT_3 concentrations have limited practical value in the diagnosis of CH.

Hypothalamic-pituitary hypothyroidism is more difficult to diagnose. The disorder is characterized by a low serum T_4 concentration with a normal range TSH value. The low-T_4–low-TSH pattern most commonly reflects prematurity or a low-TBG concentration. Measurements of serum TBG or free T_4 concentrations will distinguish these possibilities. An infant or child with a low free T_4 concentration and low TSH level should be carefully examined for evidence of hypothyroidism, and other tests of pituitary function should be conducted. A subnormal TSH response to TRH confirms a diagnosis of pituitary TSH deficiency. If the peak level of TSH is normal or prolonged and there is good 4-hour T_4 (thyroid) response to TSH, hypothalamic TRH deficiency can be inferred. The TSH deficiency may be isolated or associated with other pituitary hormone deficiencies. In these infants, treatment with T_4 raises the serum T_4 and free T_4 to normal levels.

All infants with abnormal test results should undergo radionuclide scanning if possible with either technetium (^{99m}Tc) or ^{123}I.[61] ^{123}I is preferred, if available; technetium is trapped by thyroid follicular cells but not organified. Use of radioiodine provides greater isotope concentration and allows later scanning (2 to 24 hours) with lower background radioactivity and improved discrimination. The confirmation of an ectopic thyroid gland provides a definitive diagnosis of thyroid dysgenesis. The absence of uptake of radioisotope suggests thyroid gland agenesis, but some infants may have low radioisotope uptake and a nondetectable gland by scan due to a TSH receptor defect, iodide-trapping defect, or TSH receptor blockade by maternal TBA. These infants or the mother should have blood drawn for measurement of TBA if there is a history of autoimmune thyroid disease. Thyroid ultrasound will confirm thyroid gland agenesis.

A normal radioisotope scan or a palpable or ultrasound-positive thyroid gland in the presence of hypothyroidism indicates impaired thyroid hormone synthesis.[61] Infants with mild-to-moderate TBA-mediated transient CH may have normal thyroid scan results. The maternal and family histories should be carefully reviewed in such cases. A serum Tg measurement may be helpful with infants with absent uptake or normal scans. A very low or absent serum Tg level indicates thyroid agenesis in an infant with absent radioisotope uptake and suggests a defect in Tg synthesis in infants with a normal imaging study. Infants with thyroid dysgenesis have elevated serum thyroglobulin levels, which relate to the mass of residual thyroid tissue and degree of stimulation. However, their levels usually do not exceed 1000 pmol/L (660 ng/ml). Very high levels (more than 1000 pmol/L) can occur in infants with CH due to defective thyroxine synthesis not involving the capacity for Tg production. Serum calcito-

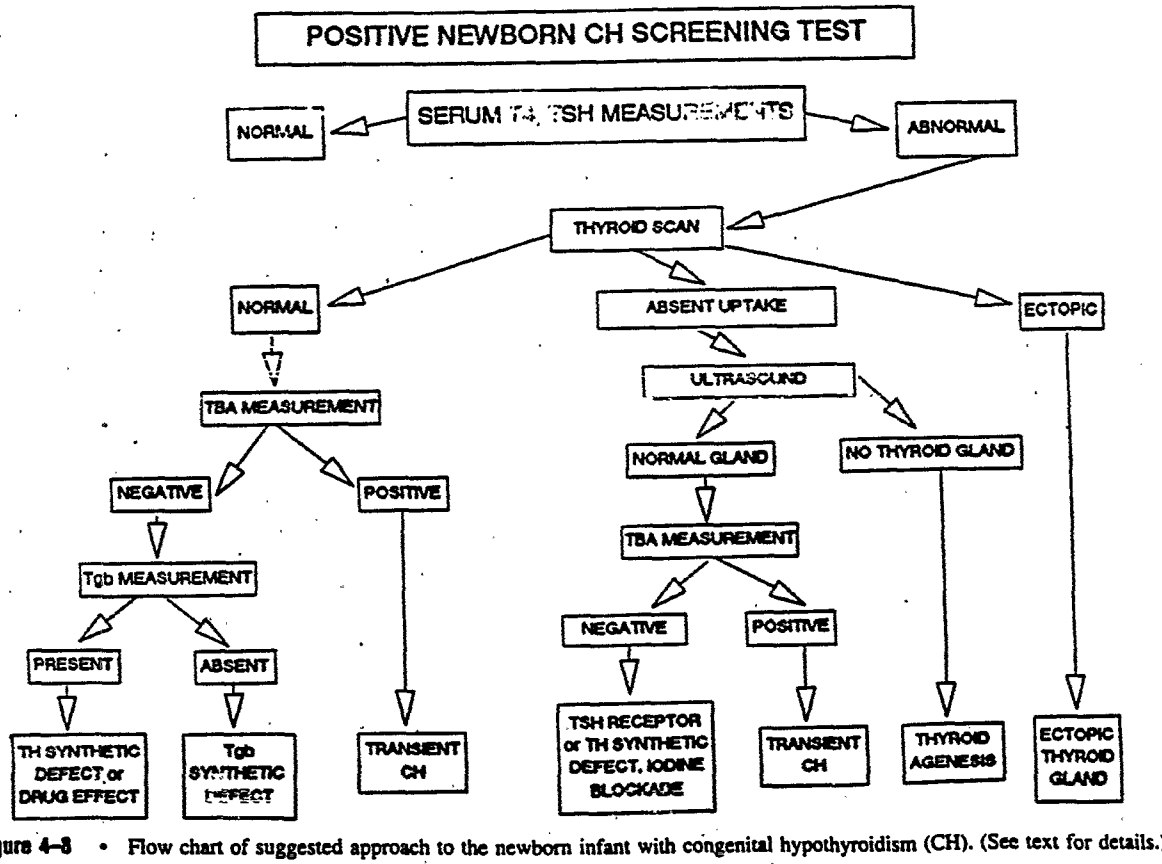

Figure 4–8 • Flow chart of suggested approach to the newborn infant with congenital hypothyroidism (CH). (See text for details.)

Table 4–3 | Normal Thyroid Function Parameters at 2 to 6 Weeks of Age

Thyroid Parameter	Normal Range
T_4	84–210 nmol/L (6.5–16.3 μg/dL)
T_3	1.5–4.6 nmol/L (100–300 ng/dL)
Free T_4	12–28 pmol/L (0.9–2.2 ng/dL)
TSH	1.7–9.1 mU/L (1.9–9.1 mU/mL)
TBG	160–750 nmol/L (1.0–4.5 mg/dL)
Tg	15–375 pmol/L (10–250 ng/mL)

nin levels also are low in CH infants with thyroid agenesis but offer no advantage over the Tg measurement in diagnosis. These approaches are summarized in Figure 4–8. Normal thyroid function test results in infants 2 to 6 weeks of age are summarized in Table 4–3. A bone age measurement (radiographic examination of the knee and foot) also is useful as a sign of possible intrauterine hypothyroidism.

Treatment of Affected Infants

The initial evaluation should be accomplished promptly and should require no more than 2 to 5 days. In the absence of facilities or funds to conduct scanning, ultrasound, TBA bioassay, or Tg measurements, treatment should be instituted as soon as the diagnosis is confirmed. The goal of newborn CH screening is the institution of early, adequate thyroid hormone replacement therapy. Most of the brain cell thyroid hormone is derived from local T_4 to T_3 conversion; approximately 70% of the T_3 in the cerebral cortex is derived via local T_4 monodeiodination. Thus, the preferred thyroid hormone preparation for treatment of infants with CH is T_4 (thyroxine).

Because the focus of screening is early and adequate treatment, the dosage of T_4 should normalize the serum T_4 level as quickly as possible.[61] To ensure adequate hormone delivery to all infants, it is desirable to maintain the serum T_4 in the upper half of the normal range during therapy. The 97% upper limit of serum T_4 levels in hypothyroid infants often reaches 130 nmol/L (10 μg/dL). For these reasons, the target range for the total T_4 concentration is 130 to 260 nmol/L (10 to 16 μg/dL). This assumes a normal serum TBG concentration. This can be confirmed by obtaining a normal-range T_3 resin uptake or TBG level at the time of the first posttreatment T_4 measurement. As an alternative, a direct free T_4 measurement can be used and should be maintained in the upper half of the normal range for the method.

To rapidly normalize the serum T_4 concentration in the CH infant, an initial dosage of Na-*l*-T_4 of 10 to 15 μg/kg/day is recommended.[61, 64] For the average term infant weighing 3 to 4.5 kg, an initial dosage of 50 μg (0.050 mg) daily is appropriate. Serum TSH concentrations in many treated infants with CH usually remain relatively elevated despite normalized levels of T_4 or free T_4. The relative elevation of serum TSH is more marked during the early months of therapy but can persist to some degree through the second decade of life.[65, 66] Increasing the total serum T_4 value to a range of 130 to 206 nmol/L (10 to 16 μg/dL) or the free T_4 to the upper half of the normal range during the first 1 to 2 years of treatment lowers the serum TSH concentration to less than 20 mU/L in most CH infants. In the remainder, the serum TSH remains at more than 20 mU/L. In these infants, raising the serum T_4 level to a range of 155 to 206 nmol/L (12 to 16 μg/dL) usually will lower the TSH value to less than 20 mU/L. The elevated serum TSH level relative to T_4 concentration in CH infants is due to a resetting of the feedback threshold for T_4 suppression of TSH release in infants with CH.[65, 66] This resetting occurs in utero, but the mechanism remains obscure. Figure 4–9 is a plot of plasma total T_4 versus TSH concentrations measured during the first 4 years of treatment in 979 children with CH.[67] All were euthyroid and growing normally. A similar plot for normal children developed from Corning Nichols Institute Clinical Correlations Department data is shown for comparison. The resetting of the feedback control threshold is clearly shown.

Physical growth and development of infants with CH usually are normalized with early adequate therapy, and infants with a delay in bone maturation at the time of diagnosis will normalize their bone age by 1 to 2 years of age. IQ levels and mental and motor development also are normalized in most infants with CH.[68–71] However, low-normal or, occasionally, low IQ levels have been reported in a small subset of CH children with very low serum T_4 and delayed bone maturation at birth.[72] This outcome has been more prevalent in programs that use a relatively low replacement dose of T_4 or in infants in whom treatment has been delayed.[64, 72] This deficit, although variable, approximates five points monthly for every month of delayed or absent treatment. Early therapy with 10 to 15 μg/kg/day of levothyroxine minimizes the early IQ loss.[73] Overtreatment

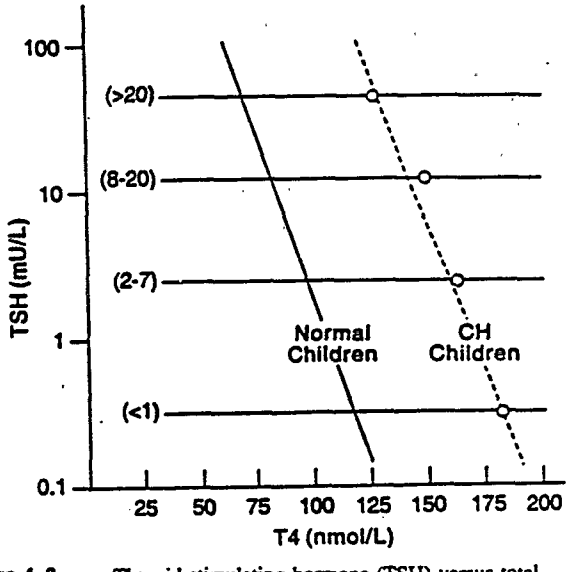

Figure 4–9 • Thyroid-stimulating hormone (TSH) versus total thyroxine (T_4) concentrations measured during the first 4 years of levothyronine therapy in 979 children with congenital hypothyroidism (CH). (Data derived from Grant DB, Fuggle PW, Smith I, et al: Congenital hypothyroidism detected by neonatal screening: relationship between biochemical severity and early clinical features. Arch Dis Child 69:555, 1993.)

can produce pathological signs, such as tachycardia, excessive nervousness, disturbed sleep patterns, and other findings suggesting thyrotoxicosis. Excessive doses over a long period produce osteoporosis, premature synostosis of cranial sutures, and undue advancement of bone age.

Infants with presumed *transient hypothyroidism* caused by maternal goitrogenic drugs need not be treated unless the low serum T_4 and elevated TSH levels persist beyond 2 weeks. Therapy usually can be discontinued after 8 to 12 weeks. Hyperthyroid mothers receiving antithyroid drugs may breastfeed their infants because the concentrations of drug in breast milk are very low. Infants with hypothyroidism secondary to maternal (transplacental) TBA also require treatment if they are hypothyroxinemic. The half-life of the maternal autoantibody approximates 2 weeks and, depending on the initial level, may require several months for degradation. Treatment usually is required for 2 to 5 months.

Infants with *thyroid resistance* are very difficult to manage, and treatment must be individualized.[74] It is important to detect infants with GRTH as early as possible to manage early relative hypothyroidism and minimize brain dysfunction, including attention deficit hyperactivity disorder. Some patients will be adequately compensated by the TSH-mediated thyroid hyperplasia and hyperthyroxinemia. Other patients will be poorly compensated, and compensation will vary among tissues.[44–46] The serum TSH level in GRTH patients may be elevated or within the normal range (albeit high in the presence of the hyperthyroxinemia). An elevated TSH level in the absence of clinical evidence for thyrotoxicosis is an indication for treatment. Failure to thrive, delayed developmental milestones, and delayed bone maturation are other indications for treatment. The levothyroxine treatment dose may be threefold to sixfold the usual replacement dose. When available, data from other involved family members can be helpful. Patients with predominant PitRTH (and elevated TSH levels) will have variable peripheral tissue responsiveness. TSH-dependent thyrotoxicosis usually presents during childhood or adolescence in such patients. Prenatal or neonatal diagnosis will become routine in affected families.

Some of the infants with GRTH have significant TSH elevation at birth in association with increased serum total and free T_4 and T_3 concentrations. Figure 4–10 shows pretreatment and posttreatment serum TSH and Tg levels and total T_4 and T_3, free T_4 index, and reverse T_3 in a newborn infant with GRTH.[43] Inital TSH approximated 50 mU/L, and total T_4 approximated 650 nmol/L (50 μg/dL). The infant manifested an enlarged thyroid gland, and serum Tg concentrations measured at 1 month approximated 0.5 nmol/L (330 ng/mL). TSH and T_4 levels fell during the first month, but TSH remained elevated, and treatment was begun at 34 days. With a levothyroxine dosage of 150 to 250 μg/day, serum TSH plateaued in the range of 5 to 10 mU/L, with total T_4 approximating 500 nmol/L.

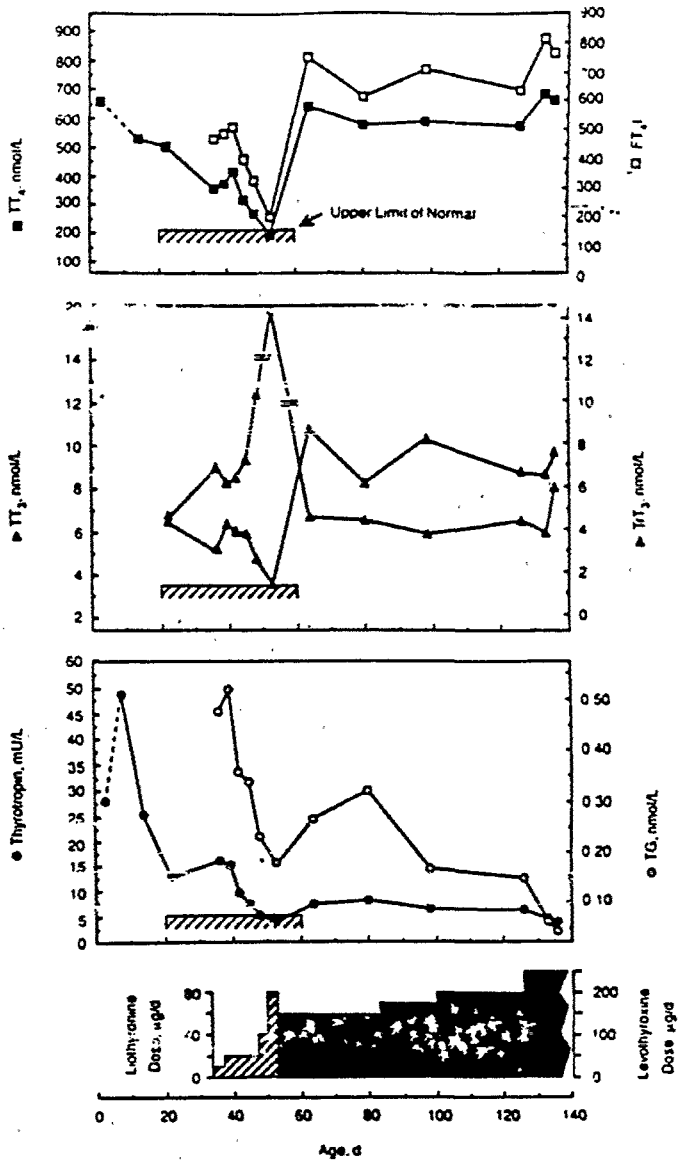

Figure 4–10 • Thyroid function parameters in an infant with generalized resistance to thyroid hormone (GRTH). Total T_4 (TT_4), free T_4 index (FT_4I), total T_3 (TT_3), total reverse T_3 (TrT_3), thyrotropin (TSH), and thyroglobulin (Tg) levels before and during levothyroxine therapy. (Reproduced with permission from Weiss RE, Balzano S, Sherberg NH, Refetoff S: Neonatal detection of generalized resistance to thyroid hormone. JAMA 264:2245, 1990.)

Congenital Hyperthyroidism

Neonatal Graves Disease

Neonatal Graves disease is uncommon because of the low incidence of thyrotoxicosis in pregnancy (1 or 2 cases per 1000 pregnancies) and because the neonatal disease occurs only in about 1 per 70 cases of thyrotoxic pregnancy.[75–78] The disease is due to transplacental passage of TSH receptor-stimulating antibody (TSA) from a mother with active or inactive Graves disease. It is possible to predict neonatal disease in offspring of women with high TSA titers. In general, TSA titers (measured as cAMP response to TSH as percent of control in a thyroid cell bioassay) of 300% to 500% are associated with a high prevalence of neonatal Graves disease.[75–78] Rarely, an infant may acquire both TSA and TBA from the mother; the blocking antibodies may block the effect of the stimulating antibodies for several

weeks, and the infant develops late-onset neonatal Graves disease.

Graves disease in the newborn is manifested by irritability, flushing, tachycardia, hypertension, poor weight gain, thyroid enlargement, and exophthalmos. Thrombocytopenia, hepatosplenomegaly, jaundice, and hypoprothrombinemia may occur. Cardiac failure and death may occur if the thyrotoxicity is severe and treatment is inadequate. The suppression of cord blood TSH values to less than 0.1 mU/L in the presence of normal or elevated levels of T_4 and T_3 suggests a TSA effect. The diagnosis is confirmed by measuring high levels of T_4, free T_4, and T_3 in postnatal blood. Cord blood values may be normal or near-normal, but levels at 2 to 5 days may be markedly increased; serum TSH is low. In some neonates, the onset of symptoms and signs may be delayed for as long as 8 to 9 days. This is due both to the postnatal depletion of transplacentally acquired blocking doses of antithyroid drugs and to the fact that there is an abrupt increase in conversion of T_4 to active T_3 by liver and other tissues shortly after birth. Neonatal Graves disease resolves spontaneously as maternal TSA in the newborn is degraded; the half-life approximates 12 days. The usual clinical course of neonatal Graves disease ranges from 3 to 12 weeks.

The treatment of hyperthyroidism in the newborn includes sedatives and digitalization as necessary. Iodide or antithyroid drugs are administered to decrease thyroid hormone secretion. These drugs have additive effects with regard to inhibition of hormone synthesis; in addition, iodide rapidly inhibits hormone release. Lugol solution (5% iodine and 10% potassium iodide; 126 mg of iodine/mL) is begun in a dosage of one drop (approximately 8 mg) three times daily. Methimazole or propylthiouracil is administered in a dosage of 0.5 to 1 mg/kg/day or 5 to 10 mg/kg/day, respectively, in divided doses at 8-hour intervals. A therapeutic response should be observed within 24 to 36 hours. If a satisfactory response is not observed, the dose of antithyroid drug and iodide can be increased by 50%. Adrenal corticosteroids in anti-inflammatory dosage and propranolol (1 to 2 mg/kg/day) may be helpful. Radiographic contrast agents also may be useful in treatment (sodium ipodate, 100 mg/day or 0.3 to 0.5 g/2 to 3 days), either alone or in conjunction with antithyroid drug treatment.[79]

Autosomal Dominant Hyperthyroidism

Several families have been reported with hyperthyroidism segregating as an autosomal dominant trait in the absence of thyroid autoimmune disease.[80] The affected individuals present with goiter, increased total and free T_4 levels, and suppressed TSH concentrations. In patients treated surgically, the thyroid glands manifest diffuse hyperplasia without lymphocytic infiltration. In two large French cohorts, TSH receptor gene mutations have been characterized involving the third and seventh transmembrane segments of the TSH receptor.[80] Functionally, the transfected mutated receptors demonstrated abnormally increased constitutive cAMP-stimulating activity.

Most affected individuals have been diagnosed during childhood or adolescence, but a few infants have been diagnosed before 2 years of age. Clearly, the abnormality is congenital, and it is possible that some of the earlier reported cases of familial persistent neonatal Graves disease have instead manifest unrecognized activating TSH receptor mutations. Treatment of such infants is difficult because the disorder is not transient. Antithyroid drugs for short-term management and partial thyroidectomy appear to be the present therapies of choice.

Disorders of Thyroid Hormone Transport

Several genetic abnormalities of the iodothyronine-binding serum proteins have been described, and all are manifest at birth; these include complete TBG deficiency, partial TBG deficiency, TBG excess, transthyretin (TTR) (prealbumin) variants, and familial dysalbuminemic hyperthyroxinemia (FDH).[81–87] Features of these disorders are summarized in Table 4–4. All are associated with a euthyroid state, but the abnormal total thyroxine concentrations can be misleading during neonatal screening and in the assessment of thyroid function.

Complete TBG Deficiency

The prevalence of TBG deficiency varies from 1 in 5000 to 1 in 12,000 newborn infants; this prevalence estimate includes infants with partial TBG deficiency (low TBG). The disorder is transmitted as an X-linked trait; serum TBG levels measured by either immunoassay or T_4-binding capacity are very low in affected males and approximately half-normal in carrier females. Serum T_4 levels vary similarly, but affected subjects are euthyroid with normal serum free T_4 concentrations, normal serum TSH levels, and normal serum TSH responses to exogenous TRH. Male-to-male transmission has not been observed, and there is invariable transmission of the trait from affected males to female offspring. There are a number of abnormalities reported and beginning characterization of the molecular defects.[37, 61] The genetic mutations lead to defective protein synthesis, to synthesis of an unstable protein, or synthesis of an abnormal protein devoid of T_4 binding and antibody recognition in immunoassay systems.

Partial TBG Deficiency

Careful studies indicate that in families with partial TBG deficiency, as in families with very low serum TBG levels, serum free T_4 and TSH levels are normal. The TBG levels are diminished in affected males, and there is a tendency for carrier females to have decreased concentrations. However, the carrier state in females is sometimes difficult to identify because of overlap with affected males or normal females. This abnormality also is transmitted as an X-linked trait.

Recent studies have indicated that partial TBG deficiency with low measured TBG concentrations by radioimmunoassay is often due to the presence of a defective TBG molecule with reduced stability. The demonstration of mutation sites and characterization of the extent of the heterogeneity in TBG deficiency must await the cloning and sequencing of the abnormal genes.

Table 4–4 Thyroid Hormone–Binding Protein Abnormalities

Abnormality	Prevalence	Inheritance	Clinical Features						Molecular Abnormality
			T_4	T_3	T_3RU	T_4 Free	Protein Level	Other	
Complete TBG deficiency	1:15,000 newborns	X-linked	Low	↓	↑	N	TBG <0.5 μg/dl	TBG absent or decreased immunoreactivity; decreased binding affinity	TBG gene mutations
Partial TBG deficiency	1:4000 to 1:12,000 newborns	X-linked	↓	↓	↑	N	↓	TBG decreased immunoreactivity or decreased stability; decreased binding affinity	TBG gene mutations
TBG excess	1:25,000 newborns	X-linked	↑	↑	↓	N	TBG ↑ 3.0–4.5 X		Defect not yet clear
Transthyretin variants	Rare	Autosomal dominant	↑	N	N	N	N	Increased T_4-binding affinity*	TTR gene mutations
			↓	N	N	N	N	Decreased T_4-binding affinity†	TTR gene mutations
Familial dysalbuminemic hyperthyroxinemia	1:100 newborns?	Autosomal dominant	↑	N	N	N	N	Increased T_4-binding affinity	Genetic polymorphism?

*Manifest in heterozygotes.
†Manifest in heterozygotes or homozygotes depending on mutation.

TBG Excess

Congenital TBG excess occurs in from 1 in 6000 newborns (in England) to 1 in 40,000 (in New York).[81] Subjects with increased levels of TBG have increased total serum T_4 concentrations with normal free T_4 and TSH levels; thus, they are euthyroid. Studies in these subjects, as in those with low TBG concentrations, have shown a correlation between TBG production rates and serum levels, suggesting that the mechanism for the high TBG concentrations is increased production, presumably by the liver. TBG levels are increased up to 4.5-fold that of normal in affected individuals, and carrier females have serum concentrations that are intermediate between normal values and the high levels of affected males. Early reports suggested a dominant mode of inheritance, but subsequent studies and review of the earlier data are compatible with an X-linked mode of inheritance. It has been proposed that the several TBG concentration abnormalities reflect mutations at a single X-linked gene locus involved in the control of TBG synthesis.

TTR Variants

Several TTR variants have been characterized in human subjects. All have been associated with altered affinity for T_4 binding, both increased and decreased.[37, 82, 83] Some of these mutations have been associated with familial amyloidotic polyneuropathy or familial amyloid cardiomyopathy. The T_4 affinity of the variants has ranged from 0.1- to 3.5-fold the affinity of the wild-type TTR. The T_3 affinity also is likely altered, but T_3 affinity for wild-type TTR is only 10% that of T_4 and 80% of T_3 normally is bound to TBG.

Familial Dysalbuminemic Hyperthyroxinemia

This binding protein abnormality was described recently by several investigators who characterized euthyroid subjects with increased serum T_4 concentrations not normalized by the use of the free T_4 index correction and with normal free T_4, total serum T_3, and TSH levels.[84–87] Thus, thyroid function parameters in these subjects resemble those in the patients with the increased affinity TTR variants. Serum thyroxine in affected subjects migrates with albumin by conventional polyacrylamide electrophoresis. The disorder appears to be transmitted as an autosomal dominant trait. There is male-to-male transmission and an affected-to-unaffected ratio of 1 or greater in first-degree relatives. A genetic alteration of the albumin molecule, increasing accessible protein cationic groups, is likely involved.[87]

The Fetus as a Patient

Advances in medical science and technology have paved the way for an increasingly direct approach to the fetus as a patient.[88] Improvements in fetal ultrasound imaging, Doppler ultrasound, and the availability and relative safety of intrauterine cordocentesis provide new windows to fetal development and metabolism. The near-term advent of fetal cell isolation from maternal blood will provide ready access to fetal DNA for molecular diagnosis. Fetal therapy via maternal transplacental drug therapy or amniotic fluid instillation is commonplace. Fetal surgery and fetal gene therapy are being pioneered.

One of the first fetal disease states directly addressed in the fetus was thyroid dysfunction. This effort was frustrated by the failure of measurements of amniotic fluid TSH and iodothyronine concentrations to reliably reflect fetal thy-

roid function. Currently, fetal thyroid size can be reliably assessed by ultrasound, and normative data for thyroid function tests have been provided for cordocentesis samples during the second half of gestation (Fig. 4–11).[13] Also, it may be possible to monitor fetal thyroid function by measurement of sulfated iodothyronine concentrations in amniotic fluid or maternal blood.[14, 89, 90] Thus, it is now possible to accurately assess and monitor fetal thyroid function and thyroid-directed therapeutic interventions in the in utero human fetus during the second half of pregnancy.

Possible indications for fetal thyroid assessment include a family history of inborn defects in hypothalamic-pituitary function or thyroid hormone metabolism, maternal drug therapy that might affect fetal thyroid function, and maternal autoimmune thyroid disease. There is increasing evidence to suggest that fetal hypothyroidism can be associated with reduction in IQ level or with brain dysfunction syndromes, and fetal hyperthyroidism is associated with brain damage, reduced fetal growth, and occasional fetal demise.[37, 72, 74, 78, 91–93] Diagnosis and treatment of fetal hypothyroidism with amniotic injection of levothyroxine and the management of fetal hyperthyroidism via maternal antithyroid drug therapy are now fairly standard procedures.[78, 94–97] Refinements will occur with increasing experience.

Conclusion

The writing of this chapter stimulated retrospection to the time and content of my first chapter, "Infantile Hypothyroidism, Diagnosis and Treatment," published in *Pediatric Clinics of North America* in November 1957. I wrote of protein-bound iodine (PBI) and butanol extractable iodine (BEI) and the availability of a new thyroid medication, Na-*l*-T_4, recently marketed by Travenol Laboratories in Morton Grove, Illinois. Classification remained confusing at the time; we talked of endemic cretins, sporadic cretins, familial goitrous hypothyroidism, and infantile hypothyroidism. The vast majority of infants with hypothyroidism were destined to have irreversible mental retardation, often severe. Until 1975, when Dr. Jean Dussault published the first article on population screening for CH, the emphasis was on early suspicion based on often subtle and nonspecific clinical features.[98] Diagnosis and treatment, however, usually were delayed 3 to 6 months; and the IQ level of treated children usually was less than 90.

The changes that have occurred in 40 years have been impressive. Classification has been resolved and includes endemic (iodine deficiency) cretinism (neurological and hypothyroid types) and sporadic CH (with etiologies as discussed in this chapter). CH due to iodine deficiency occurs in endemic goiter areas, and the term *iodine-deficiency disorders* has been developed to encompass the spectrum of manifestations of iodine deficiency (e.g., cretinism, hypothyroidism, goiter, loss of intellectual capacity) in areas of endemic iodine deficiency. Since 1974, newborn thyroid screening has been introduced to most industrialized societies, and in those societies mental retardation due to sporadic CH has been in large part eliminated. The International Council for Control of Iodine Deficiency Disorders (ICCIDD) is working worldwide with UNICEF and WHO to iodize all salt for human and animal consumption. Thyroid system ontogenesis has been studied and described in detail in several species, including humans, and the mechanism and

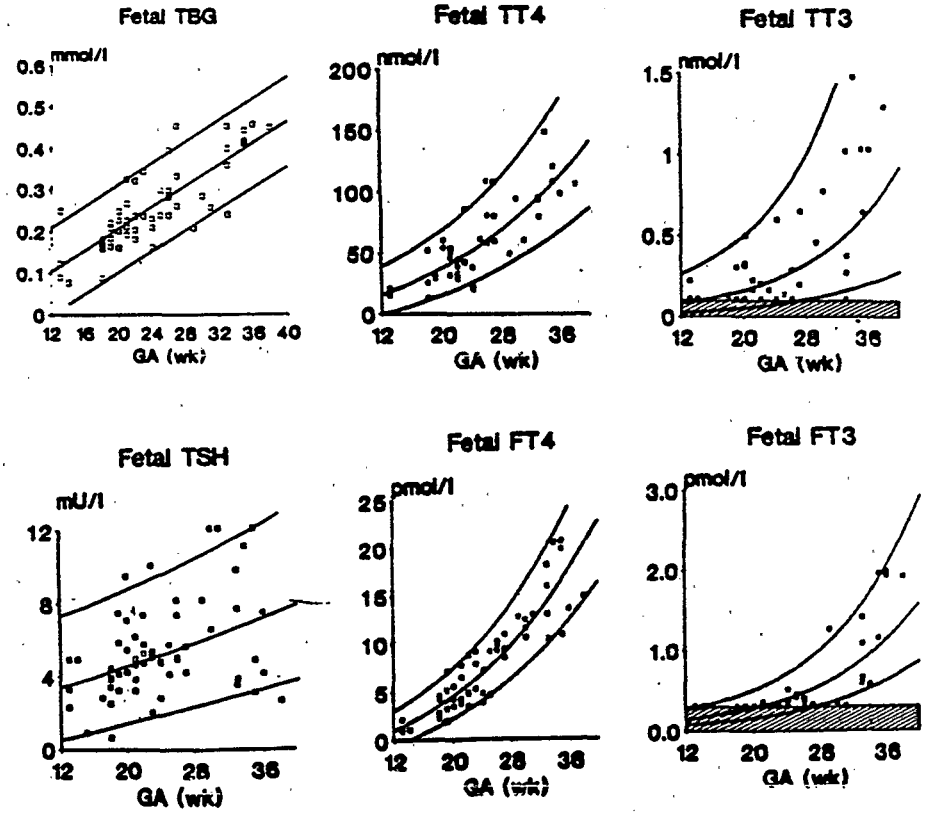

Figure 4–11 • Thyroid function test parameters in the normal in utero human fetus. Serum concentrations of TBG, total T_4 (TT_4), total T_3 (TT_3), TSH, free T_4 (FT_4), and free T_3 (FT_3) were measured in blood obtained through cordocentesis or cardiocentesis conducted for prenatal diagnosis of blood disorders, fetal karyotyping, investigation of maternal toxoplasmosis, or fetal blood grouping in red cell isoimmunized pregnancies. These values were derived from fetuses found not to have the disorder or infection in question. (Reproduced with permission from Thorpe-Beeston JG, Nicolaides KH, McGregor AM: Fetal thyroid function. Thyroid 2:207, 1992.)

impact of thyroid hormone deficiency on brain maturation represent active areas of research. The diagnosis and management of fetal thyroid disorders have come of age.

The understanding and nosology of thyroid disorders have expanded considerably, and thyroid diagnostic laboratories have responded with a dazzling array of sophisticated tests. The spectrum of autoimmune thyroid disease has been characterized, and research in pathogenesis has provided a model for human autoimmune disorders. The genes for TRH; TSH; the TRH, TSH, and thyroid hormone receptors; Tg; TPO; *Pit-1;* calcitonin; the RET oncogene, and other oncogenes have been cloned. We are rapidly approaching the era of molecular medicine applied to the thyroid patient in both diagnostic and therapeutic modes. A 40-year retrospective review of pediatric thyroidology in 2035 will undoubtedly encompass further dramatic progress.

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PEDIATRIC *Endocrinology*

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